



⁽¹²⁾ UK Patent ⁽¹⁹⁾ GB ⁽¹¹⁾ 2 356 585 ⁽¹³⁾ B

⁽⁵⁴⁾ Title of Invention

Method and apparatus for the coating of
substrates for pharmaceutical use and
intermediate products for use in producing solid
dosage forms

⁽⁵¹⁾ INT CL⁷; A61K 9/70 9/28, B05D 1/00

⁽²¹⁾ Application No
0103168.1

⁽²²⁾ Date of filing
13.11.1997

⁽²²⁾ Date Lodged
08.02.2001

⁽³⁰⁾ Priority Data

⁽³¹⁾ 9623634

⁽³²⁾ 13.11.1996

⁽³³⁾ GB

⁽⁶²⁾ Divided from Application No.
9911054.6 under Section
15(4) of the Patents Act 1977

⁽⁴³⁾ Application published
30.05.2001

⁽⁴⁵⁾ Patent published
11.07.2001

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⁽⁵²⁾ Domestic classification
(Edition S)
B2E EBD A EM E1103 E1202
E1205 E1323 E1326 E1733
E620T E620U
A5B BG BLK BLM B800 B804
B806 B807 B832 B833 B836
B841
B2L LCPA
U1S S1310 S1580

⁽⁵⁶⁾ Documents cited
None

⁽⁵⁸⁾ Field of search

As for published application
2356585 A viz:
INT CL⁷ A61K 9/20 9/28 9/70
updated as appropriate

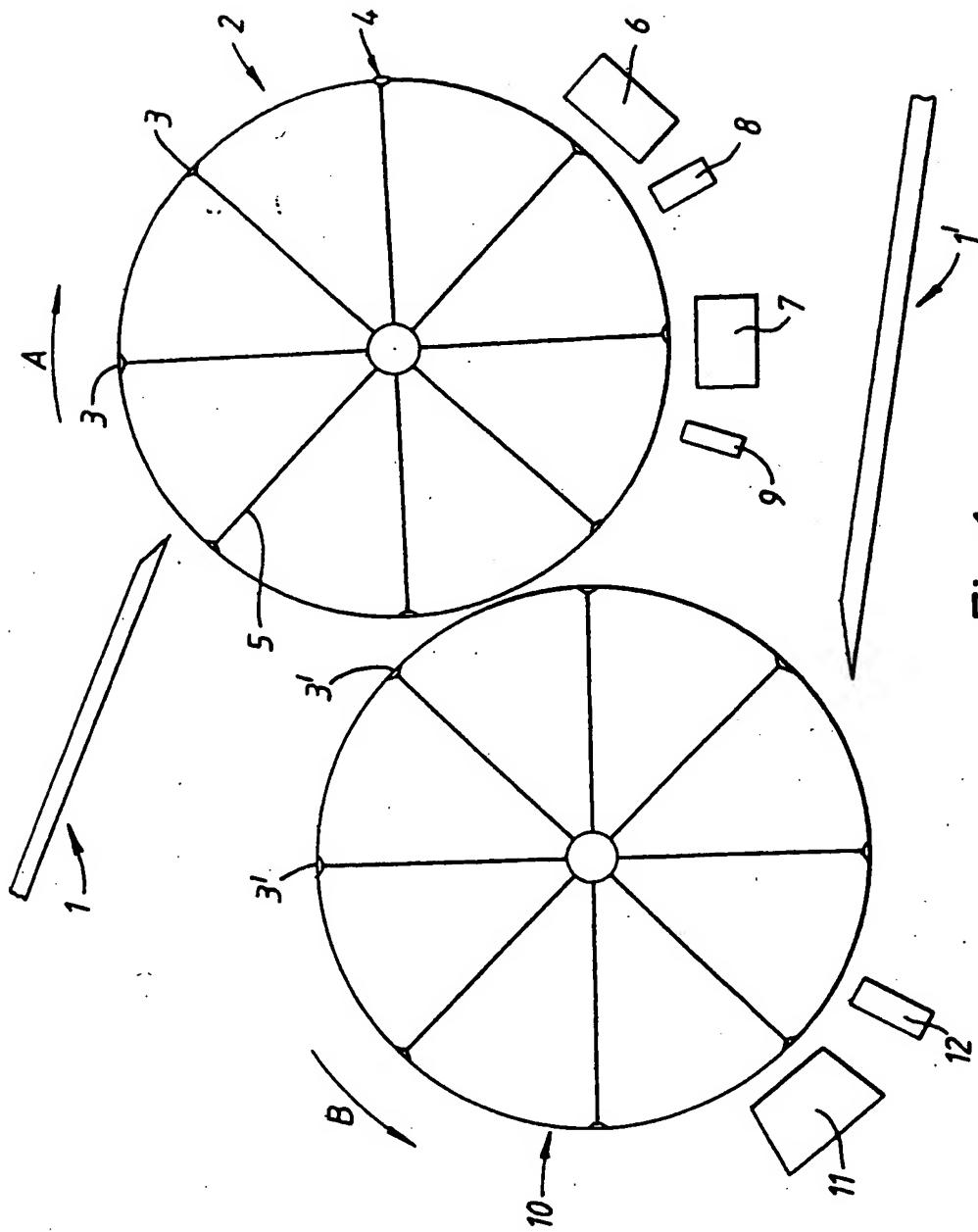


Fig.1

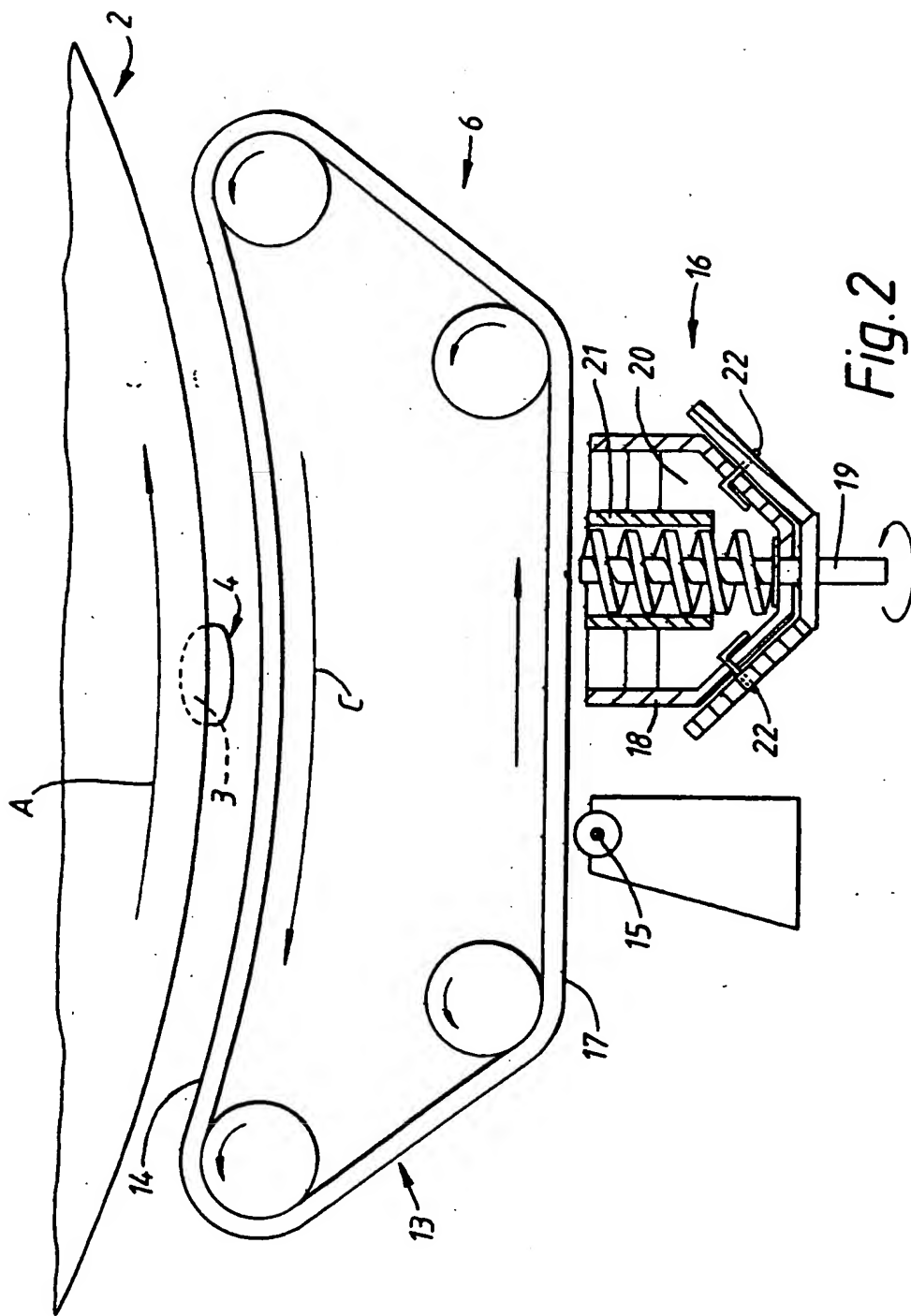


Fig. 2

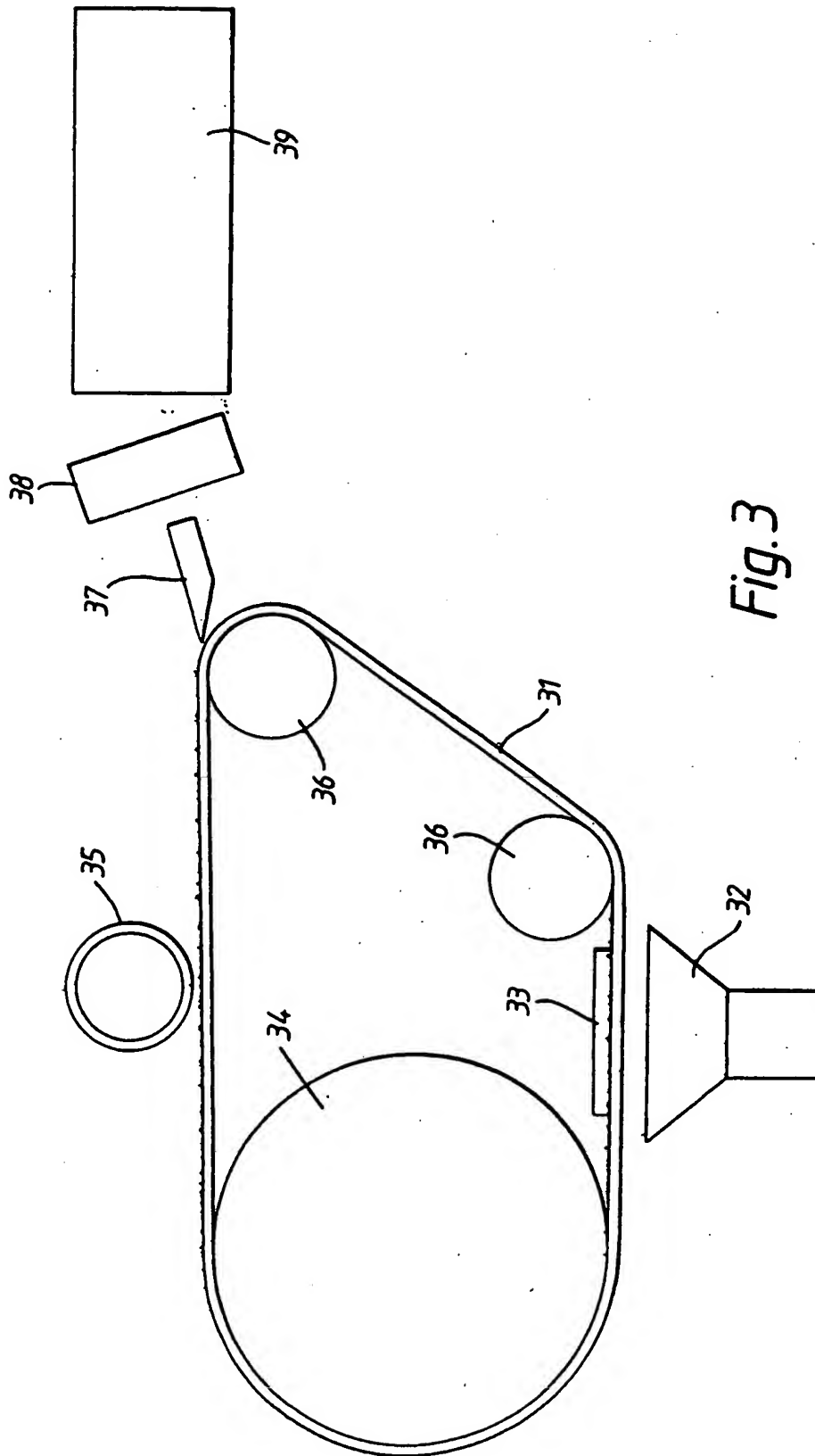


Fig.3

Method and Apparatus for the Coating of Substrates for
Pharmaceutical Use and Intermediate Products for use in
Producing Solid Dosage Forms

The present invention relates to methods of coating
5 substrates, to apparatus for coating substrates and to
coated substrates for pharmaceutical use. In particular,
but not exclusively, the invention relates to the coating
of pharmaceutical substrates to produce solid dosage
forms.

10 It is to be understood that the term "solid dosage
form" is to be interpreted in a broad sense as covering a
wide variety of pharmaceutical products. Thus the term
covers pharmaceutical products to be taken orally, for
example, pharmaceutical tablets of conventional shape as
15 well as capsules and spherules and tablets of unconven-
tional shape. The term also covers pharmaceutical
products not taken orally, for example, a pessary, a
bougie, a suppository or a patch for application to the
skin. Also, where reference is made to "pharmaceutical
20 substrate" it is to be understood that the term covers
the substrates of the solid dosage forms indicated above.
The term "solid dosage form" does not, however, include
pharmaceutical products such as small pellets and
granules, for example small pellets which are filled into
25 capsule shells for administration and granules which are
compressed to form tablets; such pellets or granules are
not themselves each solid dosage forms but rather, when
combined together in a capsule or tablet, define in
combination a solid dosage form.

30 It will be understood that the term "active
material" and "active component" used throughout the
specification includes material which is biologically
active and will comprise one or a mixture of
pharmaceutical materials. The pharmaceutical materials
35 include those materials which are administered for the

prevention and/or treatment of disease.

Active materials are conventionally administered in the form of tablets.

In a conventional method of producing a
5 pharmaceutical tablet, a mixture containing the
biologically active ingredient together with diluents
such as lactose and other ingredients is mixed and
portions of the mixture are formed into discrete tablets
by, for example, pressing samples of the mixture.

10 A problem with the method of producing tablets
described above is that, due to inhomogeneity of the
mixture from which the tablet cores are made, the amount
of active ingredient in the resulting tablet cores
varies from one tablet to the next. While that is a
15 problem for all types of tablet core produced in that
way, it is a particularly serious problem when the amount
of active ingredient in each core is low, for example for
active compounds of high activity. In that case a small
absolute variation in the percentage amount of active
20 ingredient in the cores corresponds to a significant
variation in the dose contained in each tablet which is
clearly most undesirable.

In one known method, a coating solution containing
active material is applied to the surfaces of small beads
25 using conventional spray coating techniques, for example
by spraying the coating solution towards the beads as
they are tumbled in a revolving drum. The coated beads
are filled into capsule shells for administration. Such
a method is not appropriate for use where accuracy in the
30 amount of the active material applied to the cores is
required because there is little control over the amount
of coating material applied to each core using that
method.

Active components are often administered in tablet
35 form. As indicated above, conventional tablets include a
small amount of active component and a large amount of
diluent such as lactose so that the tablet is a

convenient size. The tablet is a convenient way for the active component to be administered because each tablet contains a predetermined metered dose of the active material.

5 However, some patients find the taking of tablets difficult, for example because of their size or because of the presence of the other ingredients in the tablet composition. Thus an alternative dosage form would be desirable.

10 GB 1 561 100 describes the coating of a web with material containing an active ingredient. The coated web is processed to internalize the active coating by, for example, lamination and winding to provide a dosage form.

 It is an object of the invention to overcome or
15 mitigate one or more of the above mentioned disadvantages.

 In accordance with the invention, there is provided a method of coating a substrate, the method comprising the steps of applying an active coating material to the
20 substrate to form an active coating, the active coating material comprising biologically active material, wherein the active coating is removable from the substrate, and wherein the active coating material is applied electrostatically as a powder, and wherein the amount of active
25 coating material deposited on a given area of the substrate is controlled to allow subsequent division of the active coating into portions with each portion containing a pre-determined amount of active coating material, each pre-determined amount being one dose of
30 the biologically active material.

 In accordance with the invention, the active material is applied as a coating to a substrate from which it can be removed. The method may include the step of removing the active coating from the substrate.

35 In one embodiment of the invention, the coating material is applied directly onto a surface of the coating apparatus, the coating formed in the process

being removed from the apparatus as a wafer containing the active material.

In a second embodiment of the invention, the coating material is applied onto a substrate, the coating being removed from the substrate as a wafer, for example by a patient prior to the administration of the material. The substrate may be, for example, a sheet comprising plastics material, for example low adhesion plastics material.

10 The surface of the substrate may, if desired, be precoated with one or more coating layers.

If desired, the method of the invention may include the step of dividing the active coating into portions each containing one dose of active material.

15 The active coating material is applied electrostatically. There are various advantages in applying coating materials electrostatically, for example reduction in waste of coating material, improved coating efficiency and improved coating weight uniformity.

20 Advantageously, at least 90% by weight of the particles of the active coating material have a particle size less than 200 μ m.

Advantageously, at least 90% by weight of the particles of the active coating material have a particle size between from 1 to 200 μ m. Preferably, at least 90% by weight of the particles of the active coating material have a particle size between from 1 μ m to 100 μ m. The term "particle size" refers to the equivalent particle diameter of the particles and may be measured using, for example, laser light diffraction. The particle size of the powder is an important factor in powder coating techniques. If the particles of the powder are very small, the powder will often be too cohesive for successful powder application using many powder coating techniques. However, large particles can be disadvantageous because they are often more difficult to coat onto a surface and, if the coating material is to be

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fused after application to the surface, longer fusing times may be required, leading to increased risk of damage to the substrate and to the active component.

Where reference is made to % by weight of particles, for example the % by weight of particles having a particular size, the particles will also preferably have that % by volume of particles of that size.

Advantageously, the active coating material further includes one or more excipients. The formulation will usually consist of the active component and a mixture of excipients that will aid in the coating of the material. The formulation may also include other components, for example colorants and/or flavourings and/or agents to control the rate of release of the active component.

Advantageously, the substrate is conveyed through a region adjacent to a source of the active coating material. That allows the method to be continuous.

In one advantageous embodiment of the invention, the method comprises supporting the substrate adjacent to the source of the active coating material with a surface of the substrate maintained at such a different electric potential from that of the active coating material that the application of the electric potential causes the active coating material to move from the source of the active coating material towards the substrate, a surface of the substrate becoming coated with the active coating material.

Preferably, the substrate is supported from above and the powder moves from the source upwards towards a lower surface of the substrate.

Preferably, the substrate is charged when the substrate is adjacent the source of the active coating material. Alternatively, or in addition, the source of active coating material may be charged.

The method may further include the step that after the active coating layer is applied the active coating material is treated to form an active film coating on the

surface of the substrate. The treatment advantageously comprises a heating step, preferably by infra red radiation, but other forms of electromagnetic radiation may be used. Usually, the change in the coating upon
5 heating will simply be a physical change from a powder to a liquid and then, on cooling, to a solid coating, but there are other possibilities: for example, the powder coating may comprise a polymer which is cured during the treatment step, for example by irradiation with energy in
10 the gamma, ultra violet or radio frequency bands, to form a cross-linked polymer coating. Preferably, however, the method comprises application of the active material as a dry powder and fusion to form an active film coating on the surface of the substrate.

15 The method may further include the step of applying a cover coating layer onto the active coating layer to form a cover coating layer such that the active coating layer is substantially completely covered by the cover coating layer.

20 The active coating material applied to the surface of the substrate might not be treated to form an active film coating. A cover coating layer applied subsequently over the active coating material could be used to seal the active coating, being removable with the active
25 coating.

Advantageously, the method further includes the step that after the cover coating layer is applied the cover coating material is treated to form a film coating on the surface of the substrate. The treatment of the
30 cover coating layer may be similar to that of the active coating layer described above. Where the cover coating material is in the form of a liquid, however, the treatment advantageously comprises drying the coating material with a heater although other methods could be
35 used.

The coating material containing the active component is susceptible to damage at high temperatures and it is

therefore particularly important that the temperature of treatment to form an active film coating or to form a cover film coating is not high. Advantageously, the temperature of treatment is less than 250°C, preferably
5 less than 200°C and more preferably less than 150°C. Where the higher treatment temperatures are used, the duration of the treatment is advantageously short to reduce the possibility of damage of the coating material.

Preferably, the cover coating material is applied
10 electrostatically. The cover coating material may be in the form of a powder. The cover coating material may also include active material. The active material in the cover coating may be the same as or different from the active material in the active coating layer.

15 Advantageously, at least 90% by weight of the particles of the cover coating material have a particle size between from 1 to 200µm.

Preferably, the substrate is conveyed through a region adjacent to a source of the cover coating
20 material.

In one advantageous embodiment of the invention, the method comprises supporting the substrate adjacent to the source of the cover coating material with a surface of the substrate maintained at such a different electric
25 potential from that of the cover coating material that the application of the electric potential causes the cover coating material to move from the source of the cover coating material towards the substrate, a surface of the substrate becoming coated with the cover coating
30 material.

Advantageously, the substrate is supported from above and the powder moves from the source upwards towards a lower surface of the substrate.

Preferably, the substrate is charged when the
35 substrate is adjacent to the source of the cover coating material. Alternatively, or in addition, the source of cover coating material may be charged.

In an embodiment of the invention the active coating layer covers only part of a surface of the substrate. In that embodiment, the cover coating layer may cover only part of a surface of the substrate, or alternatively may
5 cover the whole surface of the substrate.

The cover coating layer may be applied by depositing powder which thereafter forms a layer over the active coating layer or by applying a preformed sheet or film over the active coating layer.

10 The method may further include the step of applying a further coating material to a surface of the substrate to form a further coating layer. The further coating material may include biologically active material, the further coating layer forming a further active coating
15 layer and the method may further include the step of applying a further cover coating material onto the further active coating layer to form a further cover coating layer such that the further active coating layer is substantially completely covered by the further cover
20 coating layer.

Thus substrates having two or more different active components may be produced. The cover coating material covering the first active coating may be different from that covering the second active coating so that the rate
25 of release of the first active component may be different from that of the second active component. Alternatively, the two active components may be the same and the cover coatings may be the same or different materials. One or more of the cover coating materials may contain active
30 material.

Advantageously, the method is continuous. In practice, there are considerable advantages in being able to operate the coating process continuously rather than as a batch process.

35 Advantageously, the active coating material is applied to a part of a surface of the substrate, the active coating layer forming a first active coated region

on the surface of the substrate. Where, for example, a plurality of coating layers are to be applied to each substrate, each coating layer forms a coated region on a part of the substrate.

5 Thus the method may include the further step of applying a second active coating layer onto a surface of the substrate, the second active coating layer forming a second active coated region on a surface of the substrate.

10 Preferably, the method further includes the step of applying a cover coating material onto the active coating layer to form a cover coating layer such that the active coating layer is substantially completely covered by the cover coating layer and such that the cover coating layer
15 is removable from the substrate. Depending on the nature of the cover coating material, the cover coating layer may be removable together with the active coating layer or may be removable separately. The cover coating layer provides a cosmetic coating and may also protect the
20 active coating material. The cover coating material may also include active material which may be the same as or different from the active material of the active coating layer. The cover coating may comprise a preformed film or sheet of material which is applied over the active
25 coating.

Where more than one active coating layer is applied to the substrate, the method preferably further includes the step of applying a second cover coating layer onto the second active coating layer to form a second cover
30 coating layer such that the second active coating layer is substantially completely covered by the second cover coating layer, the second cover coating layer being substantially separate from the first cover coating layer.

35 In one embodiment of the invention active powder coating material is applied to a surface of the substrate to form a plurality of active coating regions on the

surface comprising active coating layers and cover coating material is applied to a surface of the substrate to form a plurality of cover coating regions, the cover coating regions forming layers of cover coating material, 5 each active coating region being substantially completely covered by a cover coating region, each region of active coating and cover coating being removable from the surface of the substrate.

The present invention also provides a method of 10 coating a substrate, the method comprising applying an active coating material to a surface of the substrate to form an active coating layer, the active coating material comprising biologically active material, wherein the active coating layer is removable from the substrate, and 15 wherein the active coating material is applied electrostatically as a powder, applying a cover coating layer over the exposed surfaces of the active coating layer and dividing the coated substrate to form substrate portions, each substrate portion including substantially one dose 20 of the biologically active material.

The invention further provides a method of coating a substrate, the method comprising the steps of applying an active coating material to the substrate to form an active coating layer, the active coating material 25 comprising biologically active material, wherein the active coating layer is removable from the substrate, and wherein the active coating material is applied electrostatically as a powder, and wherein the active coating layer is cut into smaller portions.

30 Advantageously, the method further includes the step of removing that active coating layer from the substrate to form a wafer or wafers comprising active material which may be subsequently cut to form wafer portions, each wafer portion including substantially a dose of 35 active material.

Where reference is made to the quantity of active coating material being substantially equal to a dose of

the active material, it will be understood that the quantity may be a fraction of the single standard dose, for example $1/2$ or $1/3$ of a single standard dose of the active material. It will be understood that the quantity
5 of active material will depend on the active component used and the number of solid dosage forms to be taken by the patient for each dose. Where more than one layer of the active coating material is to be applied to each substrate, the quantity of active component in each layer
10 will be chosen accordingly.

The invention also provides apparatus for coating a substrate according to a method as described above, which comprises:

(a) a source of active powder coating material, the
15 active coating material comprising biologically active material,

(b) support means for supporting a substrate adjacent to the source of the active coating material,

(c) means for electrostatically applying the active
20 powder material to the substrate such that the active coating material forms an active coating layer on a surface of the substrate, and such that the active coating layer is removable from the substrate, and

(d) means for dividing the coated substrate or
25 active coating layer removed from the substrate to form portions each containing one dose of the biologically active material.

Advantageously, the apparatus further comprises:

(e) a source of a cover coating material,
30 (f) means for conveying the substrate having the active coating layer to a position adjacent to the source of cover coating material,

(g) means for applying the cover coating material to the active coating layer such that the cover coating
35 material forms a cover coating layer which substantially completely covers the active coating layer.

The apparatus advantageously includes means for

applying the cover coating material electrostatically. The active coating material and cover coating material may both be applied in the form of a dry powder. In a different embodiment, the active coating material may be
5 applied in the form of a dry powder and the cover coating material applied in the form of a liquid.

Advantageously, the substrate comprises a conveyor belt.

Advantageously the apparatus further includes means
10 for applying a charge to the source of active coating material. The charge can be adjusted to change the amount of coating material applied to the substrate.

Advantageously, the apparatus further includes charging means for applying a charge to the substrate.
15 The charge may be applied using a corona charge wire adjacent to the substrate or by arranging a charged plate adjacent to the substrate. The charged substrate attracts coating material from the source onto the surface of the substrate. Thus it is possible to obtain
20 a very thin uniform layer of coating material on the substrate surface.

Preferably, the source is arranged below the conveyor.

Also provided by the present invention is an
25 apparatus for coating a substrate, the apparatus comprising:

- (a) a source of active powder coating material, the active coating material comprising biologically active material,
- 30 (b) means for moving the substrate relative to the source of coating material,
- (c) means for electrostatically applying an active powder coating material onto a surface of the substrate to form a plurality of active coating regions comprising
35 active coating layers,
- (d) means for applying a cover coating material onto the surface of the substrate to form a plurality of

cover coating regions such that each active coating region is substantially completely covered by a cover coating region,
the coating materials being applied such that the active
5 coating layers are removable from the surface of the substrate, and

(e) means for dividing the coated substrate or active coated layer removed from the substrate into portions, each containing one dose of the biologically
10 active material.

The invention also provides an intermediate product for use in producing a plurality of solid dosage forms, the intermediate product comprising a substrate and an active fused coating comprising biologically active
15 material that has been electrostatically deposited as a powder on the substrate, the amount of active coating material deposited on a given area of the substrate being controlled such that the product can subsequently be divided into portions with each portion containing a
20 predetermined amount of active coating material, each predetermined amount being one dose of the biologically active material, and the active coating being removable from the surface of the substrate.

The active coating may subsequently be cut into
25 small portions.

On division, each active coating layer comprises a quantity of biologically active material which is substantially equal to one dose or, for example, one half dose of the biologically active material. It will be
30 understood that the quantity of active component will depend on the active material used and the required dose.

Preferably, the substrate further includes a cover coating layer on a surface of the substrate, the cover coating layer substantially completely covering the
35 active coating layer in which the cover coating layer is removable from the surface of the substrate. As indicated above, the cover coating layer may be removable

separately from the active coating layer.

The substrate may include a plurality of active coating layers forming active coating regions on a surface of the substrate.

5 Preferably, each active coating region includes a cover coating region comprising a layer of cover coating material in which each active coating region is substantially completely covered by a cover coating region.

10 In one embodiment of the present invention, the active coating material is applied as a metered dose to a surface of the substrate, to form an active coating layer on the surface.

Very accurate application of the coating material on each surface can be obtained.

15 This is to be contrasted with the known methods where coating material is sprayed towards the substrates. In that case the amount of coating material applied to each substrate depends on many factors all of which would require close control if accurate application is to be
20 achieved. It will be understood that whilst reference is made to applying a metered dose, that should not be taken to imply that there is necessarily any measurement of the amount of material applied.

25 Advantageously the coating method is such that the coefficient of variation of the quantity applied to each substrate or region of the substrate is not more than 15%.

30 As indicated above, where the coating material includes active material, the accuracy and reproducibility of the application of the material to the substrates is of particular importance. For known spraying techniques such as those described above, the coefficient of variation can be 50% or more. Whilst that is acceptable where the coating is a cosmetic coating, it
35 is not acceptable where the coating contains active material. Preferably the coefficient of variation is not more than 10%, and most preferably 3% or less.

In one embodiment of the invention, the area of the surface of the substrate covered by the active coating layer is less than 40% of the total surface area of the substrate. The area covered by the active coating layer
5 may be less than 25% of the total surface area of the substrate. The active coating may form a plurality of small coated regions on the surface of the substrate.

Thus the active coating layer may cover only a part of the exposed surface of the substrate.

10 Where the quantity of active material to be administered using each solid dose is small, as indicated above, it is advantageous for the proportion of active component in the active coating material to be large.

By covering a smaller proportion of the surface of
15 the substrate, a smaller amount of coating material may be used. Thus the proportion of active component in the coating material may be increased.

The active coating material may be applied to a plurality of individual regions of the surface of the
20 substrate.

The invention also provides a solid dosage form made by a method of the invention which includes the steps of removing the active coating from the substrate and of dividing the coated substrate or the active coating
25 removed from the substrate.

The pharmaceutical solid dosage form may, for example, comprise a substrate and an active coating layer covering less than 25% of the surface area of the substrate, the active coating layer comprising
30 biologically active material.

The coating layer may be shaped, for example to form a pattern, a picture, symbols, letters or numerals.

A wafer for administration to a patient, the wafer comprising biologically active material and having a
35 thickness of less than 2mm, should especially be mentioned. Preferably the thickness is less than 1mm.

In accordance with the further aspect of the

invention, the active coating layer, although removable from the substrate, is not removed therefrom. For example, the active material might be applied to an edible film which can be administered orally.

5 Embodiments of the invention will now be described by way of example having reference to the drawings of which:

- Figure 1 shows schematically a side view of an apparatus for coating a tablet core;
10 Figure 2 shows schematically a side view of a part of the apparatus of Figure 1; and
 Figure 3 shows schematically a side view of an apparatus for coating a substrate
15 in accordance with the invention.

The apparatus shown in Figure 1 is for coating both faces of pharmaceutical tablet cores. The apparatus comprises an inclined tablet core feed chute 1 leading to
20 a first rotatable wheel 2 having circular depressions 3 in its outer surface. The cores 4 are fed from the chute 1 into the depressions 3 where they are held by suction by means of a suction line 5 in communication with the base of the depression 3 via an opening. The first drum
25 is rotated in the direction shown by the arrow A. Adjacent to the outer surface of the wheel 2 downstream from the feed chute 1 is an active coating station 6 and a cover coating station 7. Downstream from the active coating station is an active coating fusing station 8 at
30 which the active coating is fused and downstream from the cover coating station 7 is a cover coating fusing station 9 at which the cover coating is fused. A cooling station (not shown) may be provided downstream from each of the fusing stations 8, 9 where cool air is directed at the
35 core to cool the fused coating.

A second wheel 10 similar to the first wheel 2 is arranged adjacent to the first wheel 2, the nip between

the wheels being downstream of the fusing station 9. The second wheel 10 rotates in an opposite sense to that of the first wheel 2 as shown by the arrow B. Arranged adjacent to the outer edge of the second wheel 10

5 downstream from the nip of the two wheels are a second cover coating station 11 and a second fusing station 12.

Figure 2 shows the active coating device 6 in more detail. Figure 2 shows a portion of the wheel 2 together with a core 4 in a depression 3 on the surface of the
10 wheel 2. As described below, the apparatus of Figure 2 can be used to form wafers of coating material in accordance with the present invention.

The active coating station 6 comprises a conveyor 13 arranged in a loop in a vertical plane so that the upper
15 surface 14 faces the surface of the wheel and the cores 4 which pass the device 6 as the wheel rotates. The contour of the upper surface 14 of the conveyor 13 is chosen to match the contour of the outer surface of the wheel so that the distance between the core and the upper
20 surface of the conveyor is unchanged as the wheel rotates. The direction of rotation C of the conveyor 13 is such that the direction of movement of the upper surface of the conveyor is opposite to that of the movement of the core over the upper surface of the
25 conveyor. Alternatively, the direction of movement of the upper surface of the conveyor and the core may be the same.

As shown in Figure 2, a corona charge wire 15 and a powder source 16 are arranged beneath the conveyor
30 immediately below the lower surface 17 of the conveyor.

The corona charge wire 15 sprays charge onto the lower surface 17 of the conveyor. It will be appreciated that a different method could be used to apply charge to the conveyor.

35 The powder source 16 uses an archimedes screw to form a small mound of powder beneath the lower surface of the conveyor. The source 16 comprises a hopper 18

containing the powder including the biologically active component, and an Archimedes screw 19 which in use passes through the powder material 20 in the hopper 18 and through a vertical barrel 21. Thus, the powder material
5 20 is circulated from the lower regions of the hopper 18 to the top of the barrel 21 where a moving heap of powder is formed. The heap will be of substantially constant size and shape as excess powder overflows from the top of the barrel 21 and is returned to the hopper 18.

10 Stirrers 22 are provided in the hopper 18 to help to improve the flow of the powder and break up any agglomerates.

 Thus a small moving heap of powder of substantially constant size and shape is formed beneath the lower
15 surface of the conveyor 17.

 It will be appreciated that a device other than the Archimedes screw could be used to form the heap of powder.

 The powder source 16 is located downstream from the
20 charge spraying device 15 and powder from the heap of powder is attracted to the surface of the charged conveyor 17 where it forms a thin, uniform layer which is transported to the upper surface 14 of the conveyor.

 The tablet core 4 passing over the upper surface of
25 the conveyor is held at a different potential from that of the conveyor 13, either by earthing the core or applying a charge to the core, and powder on the conveyor moves from the conveyor to the exposed surfaces of the tablet core 4 to form a powder coating.

30 The active coating station 6 is enclosed in a housing (not shown) to reduce the risk of powder loss of the active powder. In use the housing has an opening above the upper surface of the conveyor 14 so that the tablet core 4 is exposed to the active powder coating
35 material as it passes the station 6.

 It will be appreciated that the thickness of the powder layer formed on the surface of the tablet core

depends on several factors including the amount of charge sprayed onto the conveyor, the magnitude of the charge applied to the core, the size of the heap of powder produced, the size of the opening in the housing and the speed of the conveyor. Those factors will be varied to give the desired coating depending on the type of powder and core used.

The composition of the active coating material used will of course depend on the active ingredient to be used and the amount of the coating to be applied.

Active materials most suitable to be applied to the tablet include those materials having a high therapeutic activity, for example those where the usual prescribed dose is about 1mg or less, and which have a good stability to degradation due to heat where the coating material containing active material is to be heated.

An active material which may be applied to a tablet core in accordance with the invention is diltiazem HCl.

The amount of active ingredient to be coated onto each core or other substrate will generally be small and the active ingredient will usually be diluted with one or more excipients. The excipients used will be chosen so that they aid the coating of the active material onto the cores by, for example improving the electrostatic properties of the powder and its physical properties and aiding the formation of the fused active coating, for example the excipient may be a material which melts at a low temperature to aid the formation of a film.

The active coating material is a powder and the particle size will be an important factor with regard to the transfer of the active coating material from the conveyor to the tablet core and to the subsequent fusing of the material. Usually a particle size range of 1 to 200 μ m will be used (at least 90% of the particles of the powder having a size within that range).

One example of an active coating material is as follows:

Xylitol	45% wt
Diltiazem HCl (active)	45% wt
TiO ₂	9% wt
Colloidal silica	1% wt

5 It is thought that in at least one embodiment of the invention, the active composition will comprise three main components together with additives.

 The components may, for example, comprise the following

- 10 i) a continuous phase component, for example xylitol or PEG 6000,
 ii) the active component,
 iii) a particle seed and/or charge modifying component, for example TiO₂ or silica,
15 iv) a flow aid, for example colloidal silica or magnesium stearate.

 Each component may comprise one or more different materials.

 The active coating material of the above example was
20 in the form of a powder and had a particle size distribution such that at least 90% wt of the particles had a size in the range of from 5 to 25 μ m.

 It is often preferred that at least 90% by weight of the particles have a size in the range of from 1 to 45 μ m.
25 In one preferred embodiment 90% by weight of the particles have a size less than 70 μ m, 50% by weight have a size less than 40 μ m and 10% by weight of the particles have a size less than 10 μ m.

 The active powder coating material may be produced
30 using one or a combination of the following processing steps:

- a) precipitation of two or more of the components to form composite particles
 b) spray drying of two or more of the components to
35 form composite particles
 c) granulation
 d) extrusion

e) micronisation.

For example, all of the components of the composition may be co-micronised to give a powder material having the desired particle size.

5 An example of a powder cover coating material is as follows:

	39.75%	Eudragit* RS (ammonio-methacrylate copolymer)
10	39.75%	Klucel* (hydroxy propyl cellulose)
	15.0%	Titanium dioxide
	5.0%	Aluminium lake
	0.5%	Aerosil* 200 (colloidal silicon dioxide)

15 The cover coating material was prepared by the following method:

a) A sample containing the % wt of components listed above was premixed in a high shear mixer. Water was added to the mixture in a high shear mixer for a few
20 minutes to give a granulated mixture which was dried in a fluid bed drier at a temperature of about 45°C for 20 to 30 minutes to give a material having a moisture content (measured as loss on drying) below 3% by weight. The material was impact milled and then micronised using a
25 fluid energy mill to a powder containing particles having a size distribution such that 50% by volume of particles were of a size less than 20µm.

The cover coating material will usually include components to control the dissolution rate of the cover
30 coating to give controlled release of the active material in the active coating layer. Where more than one active coating is applied to each tablet or substrate, the release of each active coating can be different where different materials are used for the cover coating over
35 each of those active coatings.

* Eudragit, Klucel and Aerosil are Trade Marks

Where one or more of the coatings are applied as liquid coatings, a suitable liquid coating device would be used at the active coating station 6 and/or the cover coating station 7 and the fusing device would be replaced
5 by, for example a drying device to dry the liquid coating, if necessary.

In an embodiment of the invention an apparatus similar to that shown in Figure 2 is used to form wafers of coating material.

10 The apparatus comprises a conveyor belt of chemically inert material having a Teflon (RTM) coating. A corona charge wire is arranged immediately below the lower surface of the conveyor and sprays charge onto the lower surface. A powder source similar to that shown in
15 Figure 2 is also arranged beneath the lower surface of the conveyor downstream of the corona wire. The powder material in the powder source contains an active component and may have similar composition to the active powder described above. Preferably a higher proportion
20 of film-forming components are added to the powder, for example hydroxypropylcellulose (HPC).

An example of an active coating material is as follows:

	Eudragit RS (RTM)	23%
25	Diltiazem HCl (active)	40%
	HPC	25%
	TiO ₂	7%
	PEG 4000	5%

The amounts of the components are expressed as
30 percent by weight.

Powder from the powder source is attracted to the surface of the charged conveyor where it forms a thin, uniform layer of powder on a part of the outer surface of the conveyor belt. A heater is positioned downstream of
35 the powder source and the heater fuses the powder material on the conveyor surface to form a fused film

coating on the surface. The film coating is conveyed on the conveyor to a region where it is removed as a thin strip of film.

5 A cooling station may be positioned downstream of the heater to cool the film coating. The film strip removed from the conveyor may be passed to a cutting station where it is divided into portions, each of which may contain a dose of active material.

10 In an alternative embodiment of the invention, powder material is deposited onto a tape, preferably of plastics material.

While

the active material might be applied directly to a substrate from which it can be removed, it is thought that, in particular where the active material is to be peelable from the substrate in the form of a wafer, the active material would be applied to a base layer which is removable from the substrate.

20 For example, a first base coating layer would be applied to a substrate using the apparatus shown in Figure 2. Where the base coating material is applied to the substrate in the form of a powder material, the base coating would usually be fused to form the base coating layer. The base coating layer would be peelable from the substrate. One or more regions of active coating material would be applied to the base coating layer, for example using an ink jet printer head.

30 A cover coating would be applied over the active coating material. Where the cover coating is in the form of a powder, the cover coating would usually be fused to form the cover coating layer. The material would be removed from the substrate in the form of a three-layer wafer in which the active material was sandwiched between two layers. The wafer may subsequently be divided into smaller portions.

Figure 3 shows a further embodiment of the

invention.

Figure 3 shows a schematic view of an alternative arrangement of the apparatus for producing wafers including active material.

5 The apparatus is similar in operation to that described above in respect of Figure 2 and comprises a stainless steel conveyor belt 31 (which may be coated with PTFE on its external surface) mounted for rotation on three rollers 34, 36. A powder hopper 32 is arranged
10 below the conveyor 31 and wafer forming powder material is loaded into the hopper. The hopper is arranged to produce a recirculating powder bed either by fluidising the powder in the hopper with dry air or by using an
15 auger feed screw arrangement in the hopper and vibrating the powder in the hopper.

The hopper 32 is charged to from 0.5 to 10kV either positively or negatively depending on the wafer forming powder composition to be used. For the two compositions given below, the hopper would be charged negatively.

20 A plate 33 is arranged above the portion of the conveyor belt 31 which is adjacent to the hopper 32. The plate may be a stainless steel plate and is charged to a potential difference from that of the hopper 32. The plate will normally be charged to the opposite sign to
25 that of the hopper. The charge on the plate 33 may be from 0.1 to 10kV depending on the powder composition used and the thickness of the wafer to be formed.

The thickness of the layer formed on the surface of the belt will usually be from 0.5 to 3mm. The charge
30 applied to the hopper and to the plate 33, and the speed of the belt will be chosen to give the desired thickness.

The powder composition is attracted to the conveyor belt 31 and adheres to the exterior surface of the belt to form a powder layer. The size of the hopper will
35 usually be chosen so that the whole width of the conveyor belt is coated with powder. It is envisaged, however, that the powder might coat less than the whole width of

the conveyor belt 31. Also, the hopper 32 may comprise a group of several hoppers each for supplying the same or different powder compositions to the conveyor belt 31.

Thus the wafer produced using the apparatus may be a composite wafer in that it includes portions having different compositions. For example, the wafer might comprise a first layer including active material and a second coating layer including no active material.

As indicated above, the wafer might comprise a first layer including no active material, a second layer including active material and a third layer including no active material. That arrangement is particularly preferred because the active material is sandwiched between two outer layers which help to protect the active material from mechanical or chemical damage.

Such a wafer may be formed by applying a coating layer to a substrate, applying the active material to the coating layer to form an active layer and subsequently applying a cover coating layer over the active layer. The first coating layer is removable from the substrate so that a three-layer wafer is formed.

Where reference is made herein to the active material being applied to a substrate and being removable from a substrate, it will be understood that that includes the case in which the active material is applied to a coating layer which has previously been applied to the substrate, the active coating layer being removable from the substrate together with the coating layer.

The coated portion of the conveyor belt travels from the region of the hopper to the heated roller 34. The heated roller 34 is heated to slightly above the melting point of the powder composition on the surface of the conveyor belt. As the conveyor belt moves around the heated roller 34, the powder composition on the outer surface of the conveyor belt melts and forms a fused coating on the surface of the belt.

A chilled roller 35 is arranged above the conveyor

belt 31 downstream from the heated roller 34. The fused coating layer on the surface of the conveyor belt passes under the chilled roller 35 which smooths the upper surface of the coating layer and cools the coating so
5 that it solidifies to form a wafer on the exterior surface of the conveyor belt. It will be appreciated that other methods could be used to cool and smooth the coating layer, for example cool air jets arranged above the conveyor belt downstream from the heated roller 34.

10 The solidified wafer is transported on the conveyor belt 31 to the doctor blade 37 where the wafer is peeled from the surface of the belt. The conveyor belt continues around the guide rollers 36 and a further coating is deposited onto the conveyor belt as powder
15 material moves from the hopper to the belt as described above. Thus the apparatus can be used to produce a continuous wafer.

It is thought that the width of the conveyor belt would usually be up to 50cm. The material may be applied
20 across the whole width of the conveyor belt. Alternatively, the material might be applied as several bands of material across the belt, the material being supplied from several separate hoppers arranged below the belt.

25 The wafer peeled from the conveyor passes to a cutter 38 which may be a rotary knife wafer chopper where the wafer is cut into uniform pieces. The cut wafer portions may be of any shape or size but will usually contain one dose of the active material present in the
30 wafer. It will be appreciated that while circular or elliptical shaped wafer portions may be preferred from an aesthetic point of view, such shapes would lead to greater wastage of wafer material than, for example, rectangular-shaped wafer portions.

35 The pieces are then passed to a packaging station 39 where they are packaged using conventional methods to form, for example, blister packs or plasters for use as a

patch on the skin.

Examples of suitable coating compositions are given above. Particularly suitable powder compositions for use with the apparatus are as follows:

5 Composition 1

	Diltiazem HCl (active)	50%
	Eudragit* RSPO Type C	
	(ammoniomethacrylate copolymer)	47.5%
	Titanium dioxide	2%
10	Sunset yellow pigment	0.5%

The % given are % by weight. The components were mixed and the mixture was extruded and micronised to give a powder having a narrow particle size distribution below 150 μ m. For example, the particle size distribution may
15 be as follows:

10% by weight less than 20 μ m
50% by weight less than 50 μ m
90% by weight less than 90 μ m.

Composition 2

20	Diltiazem HCl	40%
	Polyethylene glycol 6000	30%
	Xylitol	20%
	Titanium dioxide	10%

The components were wet granulated together, milled
25 and sieved to form a powder having a narrow particle size distribution between 75 μ m and 20 μ m.

It will be understood that other compositions containing active material could be used. The composition will usually include from 1% to 90% by weight
30 of active material based on the weight of the

*Eudragit is a Registered Trade Mark

composition. The remainder of the formulation will usually comprise a polymeric matrix of binder material, for example Eudragit E100 (Eudragit is a Registered Trade Mark), gelatine, PVA, PVP-PVA, PEG, lactitol, 5 polypropylene. The compositions may additionally include plasticisers, opacifiers, disintegrants, detacifiers and/or pigments.

The apparatus described above may be modified so that the powder composition is deposited on a tape of 10 material which is fed around the apparatus on the exterior surface of the conveyor, the tape having a wafer coating being removed from the apparatus. The tape may be inedible, in which case the coating material may be removed from the tape on administration, where the active 15 material is to be administered orally. Alternatively, the tape may be used, for example, as a patch. Where the tape is edible, the active material may be administered without removal from the tape, for example the tape and wafer portion may be swallowed together.

Claims

1. A method of coating a substrate, the method comprising the steps of applying an active coating material to the substrate to form an active coating, the
5 active coating material comprising biologically active material, wherein the active coating is removable from the substrate, and wherein the active coating material is applied electrostatically as a powder, and wherein the
10 amount of active coating material deposited on a given area of the substrate is controlled to allow subsequent division of the active coating into portions with each portion containing a pre-determined amount of active coating material, each pre-determined amount being one dose of the biologically active material.
- 15 2. A method according to claim 1, wherein the active coating is divided into portions each containing one dose of biologically active material.
3. A method according to claim 1 or claim 2, which
20 further includes the step of removing the active coating from the substrate.
4. A method of coating a substrate, the method comprising the steps of applying an active coating material to the substrate to form an active coating layer, the active coating material comprising
25 biologically active material, wherein the active coating layer is removable from the substrate, and wherein the active coating material is applied electrostatically as a powder, and wherein the active coating layer is cut into smaller portions.
- 30 5. A method according to any one of claims 1 to 3, wherein active coating material is applied to a plurality of individual regions on the surface of the substrate.

6. A method according to any one of claims 1 to 4, wherein the active coating is removed from the substrate to form a wafer and the wafer is cut to form wafer portions, each wafer portion including
5 substantially a dose of the biologically active material.

7. A method according to any one of claims 1 to 6, wherein the method includes the step that after the active coating material is applied the active coating material is fused to form an active film coating on the
10 surface of the substrate.

8. A method according to any one of claims 1 to 7, which includes the step of applying cover coating material onto the active coating material to form a cover coating such that the active coating material is
15 substantially completely covered by the cover coating, and such that that cover coating is removable from the substrate.

9. A method of coating a substrate, the method comprising applying an active coating material to a
20 surface of the substrate to form an active coating layer, the active coating material comprising biologically active material, wherein the active coating layer is removable from the substrate and wherein the active coating material is applied electrostatically as a
25 powder, applying a cover coating layer over the exposed surfaces of the active coating layer and dividing the coated substrate to form substrate portions, each substrate portion including substantially one dose of the biologically active material.

30 10. A method according to claim 9, which further includes the step of removing the active coating layer

from the substrate.

11. A method according to claim 9 or claim 10,
wherein the method includes the step that after the
active coating material is applied the active coating
5 material is fused to form an active film coating on the
surface of the substrate.

12. A method according to any one of claims 8 to
11, wherein the cover coating material is applied
electrostatically.

10 13. A method according to any one of claims 8 to
12, wherein the cover coating material is applied as a
powder.

14. A method according to claim 13, wherein after
the cover coating material is applied the cover coating
15 material is fused to form a cover film coating.

15. A method according to any one of claims 8 to
11, wherein the cover coating is a pre-formed film or
sheet.

16. A method according to any one of claims 8 to
20 15, wherein the cover coating is removable with the
active coating.

17. A method according to any one of claims 8 to
16, wherein the cover coating provides controlled
release of the biologically active material in the active
25 coating.

18. A method according to any one of claims 8 to
17, wherein the cover material includes biologically
active material and the biologically active material of

the active coating material and the biologically active material of the cover coating material are the same.

19. A method according to any one of claims 8 to 17, wherein the cover material includes biologically
5 active material and the biologically active material of the active coating material and the biologically active material of the cover coating material are different.

20. A method according to any one of claims 1 to 19, wherein the active coating material covers less than
10 40% of the total surface area of the substrate.

21. A method according to any one of claims 8 to 20, wherein the active coating material is applied to a part of a surface of the substrate, wherein cover coating material is applied onto the active coating
15 material to form a cover coating such that the active coating is substantially completely covered by the cover coating and covers only part of the surface of the substrate, and such that that cover coating is removable from the substrate.

22. A method according to claim 21, wherein active coating material is applied to a plurality of active coating regions on the surface of the substrate and cover coating material is applied to form a plurality of cover coating regions, each active coating region being
25 substantially completely covered by a cover coating region, such that each region of active coating and cover coating is removable from the surface of the substrate.

23. A method according to any one of claims 8 to 20, wherein cover coating material is applied onto the
30 active coating material to form a cover coating such that the active coating is substantially completely covered by

the cover coating and covers the whole surface of the substrate, and such that that cover coating is removable from the substrate.

24. A method according to any one of claims 8 to 5 23, wherein in addition to applying a cover coating material, the method further includes the step of applying a further coating material to a surface of the substrate to form a further coating such that the further coating is removable from the substrate.

10 25. A method according to claim 24, wherein the further coating material includes biologically active material, the further coating forming a further active coating.

26. A method according to claim 25, wherein the 15 method further includes the step of applying a further cover coating material onto the further active coating to form a further cover coating such that the further active coating is substantially completely covered by the further cover coating and such that the further cover 20 coating is removable from the substrate.

27. A method according to claim 26, wherein the biologically active material in the further active coating is different from that in the first active coating.

25 28. A method according to claim 27, wherein the cover coating material covering the first active coating is different from that covering the further active coating so that the rate of release of the first biologically active material from the first active 30 coating is different from that of the further active coating.

29. A method according to claim 26, wherein the biologically active material in the further active coating is the same as that in the first active coating, and the cover coating materials are the same.

5 30. A method according to claim 26, wherein the biologically active material in the further active coating is the same as that in the first active coating, and the cover coating materials are different.

10 31. A method according to any one of claims 26 to 30, wherein one or more of the cover coating materials contains a biologically active material.

15 32. A method according to any one of claims 26 to 31, wherein the method includes the step of applying a second active coating onto a surface of the substrate, the second active coating forming a second active coating region on the surface of the substrate, the second active coating being removable from the substrate, and applying a second cover coating onto the second active coating to form a second cover coating such that
20 the second active coating is substantially completely covered by the second cover coating, the second cover coating being substantially separate from the first cover coating, and being removable from the substrate.

25 33. A method according to any one of claims 1 to 32, wherein the substrate is pre-coated with one or more coating layers.

30 34. A method according to claim 33, wherein the coating layer pre-coated on the substrate is removable from the substrate and the active coating is removable therewith.

35. A method according to claim 34, which comprises applying to the substrate a base coating layer, applying the active material to the base layer and applying a cover coating layer over the active coating layer, the
5 three layers being removable together by peeling from the substrate in the form of a three-layer wafer.

36. A method according to claim 35, wherein the base coating layer and the cover coating layer are each applied as a powder and each fused to form a film.

10 37. A method according to claim 35 or claim 36, wherein the base layer and cover layer do not contain active material.

38. A method according to any one of claims 35 to 37, wherein the wafer is removed from the substrate and
15 divided into smaller portions.

39. A method according to any one of claims 5 to 38, wherein the active material is applied to a surface of the coating apparatus and the active coating is removed as a wafer.

20 40. A method according to claim 39, wherein the active material is applied to a conveyor belt.

41. A method according to any one of claims 1 to 38, wherein the substrate is a tape.

42. A method according to claim 41, wherein the
25 tape is made of plastics.

43. A method according to any one of claims 1 to 38, wherein the substrate is a sheet comprising plastics

material.

44. A method according to claim 43, wherein the plastics material is low adhesion plastics material.

45. A method according to any one of claims 1 to 5 44, wherein at least 90% by weight of the particles of the active coating material have a particle size in the range of from 1 to 45 microns.

46. A method according to any one of claims 1 to 10 45, wherein 90% by weight of the particles have a size less than 70 microns, 50% by weight have a size less than 40 microns and 10% by weight have a size less than 10 microns.

47. A method according to any one of claims 1 to 15 46, wherein the substrate is conveyed through a region adjacent to a source of the active coating material.

48. A method according to claim 47, wherein the method comprises supporting the substrate adjacent to the source of the active coating material with a surface of the substrate maintained at such a different electric 20 potential from that of the active coating material that the application of the electric potential causes the active coating material to move from the source of the active coating material towards the substrate, a surface of the substrate becoming coated with the active coating 25 material.

49. A method according to claim 47 or claim 48, wherein the substrate is supported from above and the powder moves from the source upwards towards a lower surface of the substrate.

50. A method according to any one of claims 47 to 49, wherein the substrate is charged when the substrate is adjacent to the source of the active coating material.

51. A method according to any one of claims 47 to 50, wherein the source of active coating material is charged.

52. A method according to any one of claims 1 to 51, wherein the method is continuous.

53. A method according to any one of claims 1 to 52, the method being such that the coefficient of variation of the quantity of active coating material applied to each substrate or region of the substrate is not more than 15%.

54. A method according to claim 53, wherein the coefficient of variation is not more than 10%.

55. A method according to claim 1, which is carried out substantially as described herein.

56. Apparatus for coating a substrate, the apparatus comprising:

(a) a source of active powder coating material, the active coating material comprising biologically active material,

(b) support means for supporting a substrate adjacent to the source of the active coating material,

(c) means for electrostatically applying the active coating material as a powder to a surface of the substrate such that the active coating material forms an active coating on the surface of the substrate and such that the active coating is removable from the substrate, and

(d) means for dividing the coated substrate or active coating layer removed from the substrate to form portions each containing one dose of the biologically active material.

5 57. Apparatus according to claim 56, further comprising:

 (e) a source of a cover coating material,

 (f) means for conveying the substrate having the active coating to a position adjacent to the source of
10 cover coating material,

 (g) means for applying the cover coating material onto the active coating material such that the cover coating material forms a cover coating which substantially completely covers the active coating and
15 such that the cover coating is removable from the substrate.

 58. Apparatus according to claim 56 or claim 57, wherein the substrate comprises a conveyor belt.

 59. Apparatus according to any one of claims 56 to
20 58, which includes means for applying a charge to the source of active coating material.

 60. Apparatus according to any one of claims 56 to 59, which includes means for applying a charge to the substrate.

25 61. Apparatus according to any one of claims 56 to 60, wherein the source is arranged below the substrate.

 62. Apparatus for coating a substrate, the apparatus comprising:

 (a) a source of active powder coating material, the
30 active coating material comprising biologically active

material,

(b) means for moving the substrate relative to the source of coating material,

(c) means for electrostatically applying an active
5 powder coating material onto a surface of the substrate to form a plurality of active coating regions comprising active coating layers,

(d) means for applying a cover coating material onto the surface of the substrate to form a plurality of
10 cover coating regions such that each active coating region is substantially completely covered by a cover coating region,
the coating materials being applied such that the active coating layers are removable from the surface of the
15 substrate, and

(e) means for dividing the coated substrate or active coated layer removed from the substrate into portions, each containing one dose of the biologically active material.

20 63. An intermediate product for use in producing a plurality of solid dosage forms, the intermediate product comprising a substrate and an active fused coating comprising biologically active material that has been
electrostatically deposited^{as a powder} on the substrate, the amount
25 of active coating material deposited on a given area of the substrate being controlled such that the product can subsequently be divided into portions with each portion containing a predetermined amount of active coating material, each predetermined amount being one dose of the
30 biologically active material, and the active coating being removable from the surface of the substrate.

64. An intermediate product according to claim 63, the substrate further including a cover coating on a surface of the substrate, the cover coating substantially

completely covering the active coating wherein the cover coating is removable from the substrate together with the active coating or separately.

65. An intermediate product according to claim 64,
5 wherein the cover coating has been applied electrostatically.

66. An intermediate product according to claim 64 or claim 65, wherein the cover coating is a fused film coating.

10 67. An intermediate product according to any one of claims 64 to 66, wherein the active coating covers only a part of the surface of the substrate and the cover coating covers only a part of the surface of the substrate.

15 68. An intermediate product according to any one of claims 64 to 66, wherein the active coating covers only a part of the surface of the substrate and the cover coating covers the whole surface of the substrate.

20 69. An intermediate product according to any one of claims 63 to 68, wherein the substrate includes a plurality of active coatings forming active coating regions on a surface of the substrate.

70. An intermediate product according to claim 69,
wherein each active coating region includes a cover
25 coating region comprising a layer of cover coating material in which each active coating region is substantially completely covered by a cover coating region, and each region of active coating and cover coating is removable from the substrate.

71. An intermediate product according to any one of claims 67 to 70, wherein the active coating material covers less than 40% of the total surface area of the substrate.

5 72. An intermediate product according to any one of claims 64 to 66, wherein the cover coating layer is as specified in any one of claims 16 to 19.

73. An intermediate product according to any one of claims 63 to 72, which includes one or more further
10 coatings as specified in any one of claims 24 to 32.

74. An intermediate product according to any one of claims 63 to 73, wherein the substrate is as specified in any one of claims 33, 34 and 41 to 44.

75. An intermediate product according to claim 74,
15 wherein the active coating is sandwiched between a base coating layer and a cover coating layer, the three layers being removable together from the substrate.

76. An intermediate product according to claim 75, wherein the base and cover coating layers are fused
20 layers.

77. An intermediate product according to claim 75 or claim 76, which is a three-layer wafer comprising an active material layer sandwiched between two non-active layers.

25 78. An intermediate product according to any one of claims 63 to 77, wherein the active coating material comprises

- i) a continuous phase component
- ii) the biologically active material

- iii) a particle seed and/or charge-modifying component and
- iv) a flow aid.

79. A coated substrate when made according to a
5 method according to any one of claims 1 to 55.

80. A solid dosage form when made by a method
according to any one of claims 3 to 55 which includes
the steps of removing the active coating from the
substrate and of dividing the coated substrate or the
10 active coating removed from the substrate.

81. A solid dosage form according to claim 80,
which is a wafer for oral administration.

82. A solid dosage form according to claim 80,
which is a patch for application to the skin.

15 83. A solid dosage form according to claim 80,
which is a three-layer wafer comprising an active
material layer sandwiched between two non-active layers.

84. A solid dosage form when made from an inter-
mediate product according to any one of claims 63 to 78.

20 85. A product for division into a plurality of
solid dosage forms, when made from an intermediate
product according to any one of claims 63 to 78 by
removal from the substrate.